Early Journal Content on JSTOR, Free to Anyone in the World

This article is one of nearly 500,000 scholarly works digitized and made freely available to everyone in the world by JSTOR.

Known as the Early Journal Content, this set of works include research articles, news, letters, and other writings published in more than 200 of the oldest leading academic journals. The works date from the mid-seventeenth to the early twentieth centuries.

We encourage people to read and share the Early Journal Content openly and to tell others that this resource exists. People may post this content online or redistribute in any way for non-commercial purposes.

Read more about Early Journal Content at http://about.jstor.org/participate-jstor/individuals/early-journal-content.

JSTOR is a digital library of academic journals, books, and primary source objects. JSTOR helps people discover, use, and build upon a wide range of content through a powerful research and teaching platform, and preserves this content for future generations. JSTOR is part of ITHAKA, a not-for-profit organization that also includes Ithaka S+R and Portico. For more information about JSTOR, please contact support@jstor.org.

TUBERCULOSIS OF THE PLACENTA.

A HISTOLOGICAL STUDY WITH ESPECIAL REFERENCE TO THE NATURE OF THE EARLIEST LESIONS PRODUCED BY THE TUBERCLE BACILLUS.*

ALDRED SCOTT WARTHIN, PH D., M.D.,
Professor of Pathology, University of Michigan, Ann Arbor, Michigan.

IN this *Journal* for January, 1904, the writer, with Dr. D. M. Cowie, contributed a study of placental and congenital tuberculosis based upon a case observed by them of placental tuberculosis occurring in the seventh month of pregnancy, associated with miliary tuberculosis of the mother. At the time only eight undoubted cases of tuberculosis of the human placenta could be collected from the literature. Of these, two cases had been reported by Lehmann, three by Schmorl and Kockel, two by Warthin, and one by Auché and Chambrelente. Since our paper was published a number of other cases have been recorded. Of these, one case by Runge had been reported while our article was in press; since its publication Schmorl and Geipel have added nine cases, and Wollstein one, the total number at the present thus being brought up to 20. This rapid increase in the number of reported cases bears out the belief expressed in our paper that placental tuberculosis is probably of much more frequent occurrence than is at the present time supposed, and that with more careful and systematic examinations of placentas the number of cases would increase. This view found striking corroboration in the examination by Schmorl and Geipel of placentas from 20 cases in which the mothers were tuberculous, and the demonstration of tuberculosis of the placenta in nine of these cases. The fact that the majority of reported cases were seen by but two or three observers also points to a not infrequent occurrence of the condition.

Aside from the question of its frequency and the part played by placental tuberculosis in the etiology of congenital tuberculosis, a number of problems were suggested by the histological study of our case that could not at the time be satisfactorily answered. The

---

* Received for publication May 1, 1907.

part played by the syncytium in the development of the placental lesion, the primary or secondary nature of the agglutination-thrombi in the intervillous spaces, the histogenesis of the giant-cells, the passage of tubercle bacilli through an apparently normal syncytium, etc., constituted some of the questions that it was hoped a more extended study of the material might serve to answer. The purpose of the present paper is to present the results of such a study.

Recalling briefly the clinical history of our case, the mother, aged 27, had a bad family history, her father, three aunts, and one brother having died of pulmonary tuberculosis. She herself had been a frail child. Previous to and after her marriage she had urinary difficulty. During the last year of her life she developed a dry and distressing cough with attacks of sweating. She nevertheless became pregnant, and while in the seventh month died of general miliary tuberculosis. The fetus and placenta were expelled twelve hours before death, no signs of life being shown in the child. Autopsy of the mother showed a chronic tuberculosis of the kidneys and an acute general miliary tuberculosis. The fetus, membranes, placenta, and the uterus with its appendages were secured entire for study. Animal inoculations from the fetal liver and the placenta gave positive results. Tubercle bacilli were found in numbers in the blood-vessels of the fetal liver, but no tubercles were seen in any of the fetal organs or tissues. Countless tubercles in all stages of development were found in the placenta, and numerous tubercle bacilli were demonstrated in these. Animal inoculations with placental blood also gave positive results.

The entire uterus, membranes, placenta, fetus and cord described above were preserved after the original examination, and from time to time, as circumstances would permit, a more minute and thorough study has been carried out than was at first possible. It is to the results of this study that I now wish to direct attention, particularly with reference to the changes produced in the decidua and placenta by tubercle bacilli, and at the same time to fix more precisely the character of the primary lesion of tuberculosis. The entire placenta was cut into parallel strips about 5 mm. wide. Half of these were fixed in mercuric chloride, half in 4 per cent formaldehyde, after-hardened in alcohol, and imbedded in paraffin. The uterus was cut into suitable blocks and similarly treated. During the last two years, with the assistance of advanced students, thousands of sections have been cut from this material and have been studied. A large portion of it has also been utilized as teaching material, and I have in this way been enabled to examine microscopically the greater part of the placenta and decidua of this case. From this this study I now feel that certain definite answers can be given to some of the problems mentioned above. To the laborious study of a great number of consecutive serial sections are due the conclusions herein contained. The majority of the sections were stained with hematoxylin and eosin for the histological study, although a variety of special stains was employed for different purposes. For the demonstration of the tubercle bacilli the carbol-fuchsin method was used.

Schmorl and Geipel in their work on placental tuberculosis describe it as occurring in four forms, dependent upon the localization of the tuberculous lesion: (1) on the periphery of the villi; (2) in the stroma of the villi; (3) in the basal decidua; (4) in the chorion involving the amnion as well. From my own studies of placental tuberculosis I should class the lesions as follows: (1) decidual; (2) intervillous; (3) intravillous; (4) intravascular chorionic; (5) chorio-amniotic. This agrees with the classification given by Schmorl and Geipel with the addition of the intravascular chorionic tubercles, which are due to the development of tubercle bacilli in the blood-vessels of the villi or chorionic stems, resulting in a primary lesion of the endothelium of the vessel, followed by a secondary thrombosis. The later organization of the thrombus by epithelioid cells derived from the connective-tissue of the vessel wall gives rise to an intravascular tubercle. These five types of placental tuberculous lesions will now be described in detail.

A. TUBERCULOSIS OF THE DECIDUA.

Throughout the entire decidua, in both the superficial and basal portions, there were present areas of necrosis of varying size. Many of these areas were fairly sharply circumscribed, but the majority were surrounded by a narrow zone of necrobiotic decidual cells. From the areas of necrosis found normally in the decidua of the mature placenta these necrotic foci could as a rule be distinguished by the caseous character of the necrosis and the marked karyorrhexis of the lymphocytes and polymorphonuclear leukocytes found in and about the area. They took both eosin and hematoxylin more heavily than normal necrotic areas, appeared somewhat less translucent and contained more fibrin, as was shown by staining with Weigert's fibrin method. Disintegration and diffusion of the chromatin from the decidual cells and leukocytes gave to the smaller areas, as well as to the peripheral portions of the larger ones, a diffuse blue staining with hematoxylin. The centers of many of the larger foci showed a partial liquefaction, small pockets of soft caseous matter thus being formed. This change was noted particularly in those foci containing a large number of polymorphonuclear leukocytes. The decidual lesions presented all stages of the necrotic process, from small groups of decidual cells showing beginning disintegration up to the larger areas of complete necrosis.

Associated with the necrotic areas in the decidua there were always present thrombi in the decidual sinuses or vessels, the necrotic areas usually lying adjacent to or surrounding a thrombosed vessel. The smallest of the thrombi were composed of a deep pink-staining granular or hyaline substance derived from agglutinated red-blood cells or blood-plates. Superimposed upon the hyaline thrombi laminated masses of fibrin were found in the larger vessels and sinuses. These larger thrombi often extended out into the intervillous spaces. Serial sections showed that in all cases the hyaline agglutination-thrombus rested upon or was adherent to a portion of the wall of the blood-vessel or sinus, that showed varying stages of necrobiosis or necrosis at the point of attachment. In the case of the smallest thrombi the degeneration or necrosis involved only the endothelium or syncytium of the vessel or sinus and the decidual cells lying just adjacent to the vessel wall. The varying stages of the process found and the relations between the thrombus and the lesion of the vessel wall led me to conclude that in all cases the thrombus is a secondary formation dependent upon a local injury to the vessel lining. As a result of this local lesion there is deposited upon the damaged area a mass of blood-plates and red-blood cells. These agglutinate to form a hyaline thrombus. In and about this lymphocytes and polymorphonuclear

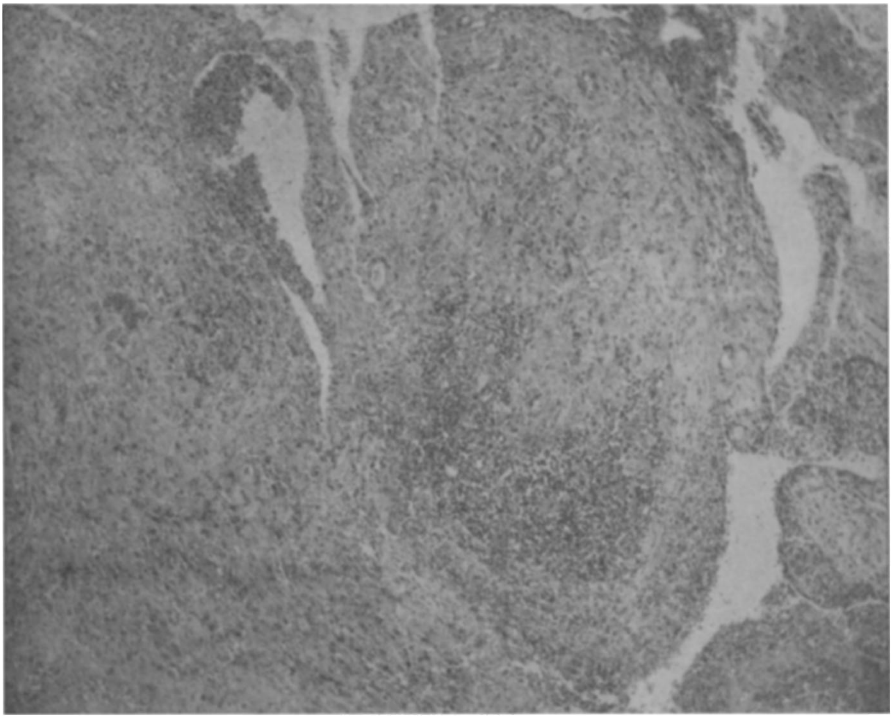

FIG. 1.—Early stage of tuberculosis of decidua. Area of beginning caseation.

leukocytes collect and quickly undergo karyorrhexis. Following these events there is a secondary coagulation with the formation of thready fibrin. With the growth of bacilli in the thrombus it undergoes caseation necrosis and this process gradually involves the neighboring decidua.

The staining of sections of the decidua with carbol-fuchsin, decolorization in nitric acid, and counterstaining in methylene-blue, showed the presence in the necrotic foci and in the hyaline thrombi of tubercle bacilli. In the very small hyaline thrombi associated with slight degenerative changes in the wall of the vessel the bacilli were found only in the thrombus; but in the larger areas of necrosis of the decidual cells the bacilli were also present in large numbers in the necrotic tissue outside of the blood-vessel. They were most numerous around the borders of the areas showing a partial liquefaction. The bacilli were also found singly throughout the fibrinous portions of the thrombi and free in the blood-vessels.

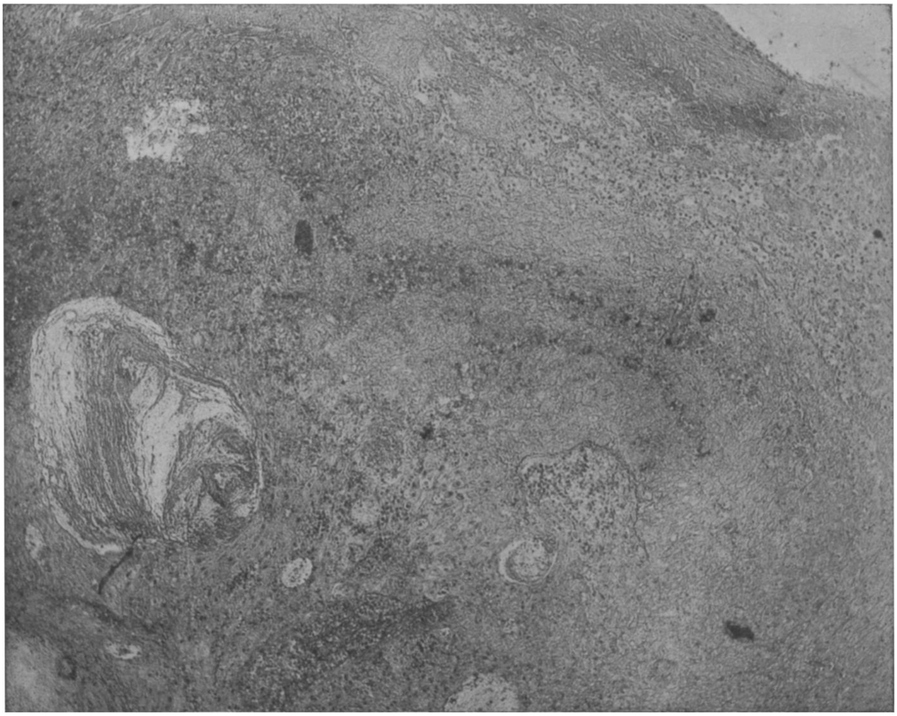

FIG. 2.—Typical area of tuberculous necrosis and thrombosis in decidua.

No evidences of tubercle-formation were found in the decidua. Epithelioid and giant-cells were wholly absent in the lesions involving only decidual tissue. In the lowest portion of the basal decidua evidences of such a reaction were seen in the connective-tissue of the uterine wall. About some of the blood-vessels a few giant-cells and a beginning epithelioid proliferation were seen, but these must be regarded as constituting a uterine tubercle and not a decidual one. Further, in the superficial portion giant-cells occurred in thrombi extending from the decidual sinuses into the intervillous blood-spaces. In this case, the giant-cells, in my opinion, originated from the stroma of chorionic villi involved in the thrombus. The decidual lesions were purely of the nature of a caseous necrosis. In the decidual septa of the placenta areas of tuberculous caseation similar to those in the basal decidua were present. These, likewise, were lacking in epithelioid and giant-cells, except where derived from neighboring chorionic villi. In all cases the necrotic foci were in close association with thrombi in the decidual vessels. The minute study, exhaustive in its thoroughness, that was accorded this case revealed not a trace of a pure decidual tubercle.

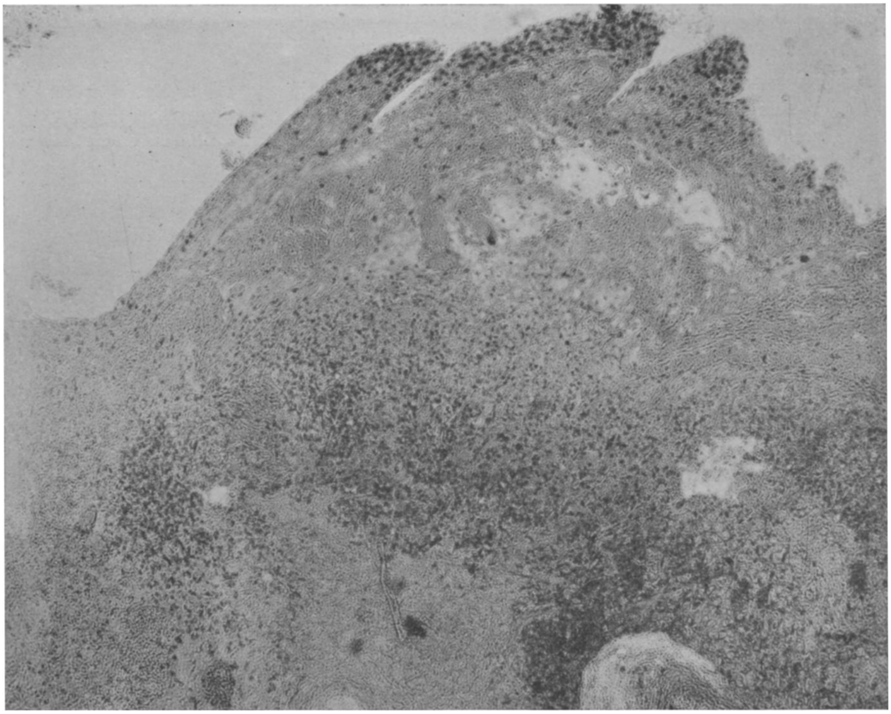

FIG. 3.—Higher power view of portion of FIG. 2; edge of tuberculous necrosis.

Such a phenomenon is, I think, not to be explained upon the ground of a very acute process, since the decidual lesions were very much more marked and apparently older than those of the intervillous spaces and chorionic villi, but in the latter the formation of epithelioid and giant-cells was the rule, even in the smallest lesions. On the contrary, then, the absence of tubercles in the decidua points rather to some individual peculiarity of decidual tissue, in so far as a reaction to infection with tubercle bacilli is concerned. In this one case, at least, under the action of developing bacilli, the decidual cells have undergone necrosis at the point of bacillary growth without the decidual tissue about the necrotic foci showing the slightest signs of a reactive proliferation such as is practically always the rule in tuberculosis of other tissues. It is true that in very acute and virulent cases of miliary tuberculosis the patient may die before the tubercle-reaction has taken place, so that at autopsy the pathological findings are those of focal necroses containing tubercle bacilli. Both factors of acuteness and virulence may be ruled out in this case, since the

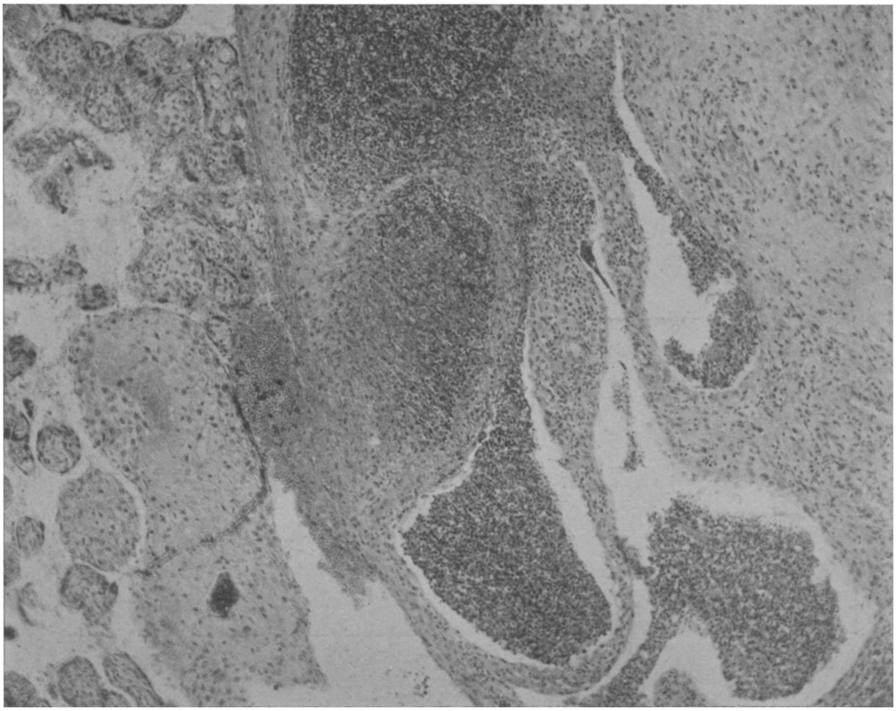

FIG. 4.—Advanced stage of tuberculosis of decidua. Partial liquefaction of tuberculous foci.

much smaller lesions in the fetal portion of the placenta showed true tubercle formation. This leaves us, then, to the conclusion that the decidual cells simply die under the action of tubercle bacilli and that they are not able to form epithelioid cells and giant-cells. The explanation of this we may seek in the more highly differentiated character of the decidual cell as compared with an ordinary connective-tissue cell.

In the second case of placental tuberculosis reported by me a similar condition was seen. The formation of epithelioid and giant-cells was limited to the stroma of the villi; but was not seen in the portions of decidua attached to the placenta. In these the tuberculous lesions were purely necrotic. These two observations may be taken as indications that tubercles are not formed in the decidua. Neither the endothelium of the decidual sinuses and blood-vessels nor the decidual cells themselves appear to have the power of forming epithelioid cells and giant-cells. Further, the absence of giant-cells from the tuberculous lesions in the decidua may be taken also as evidence against the formation of these cells from leukocytes.

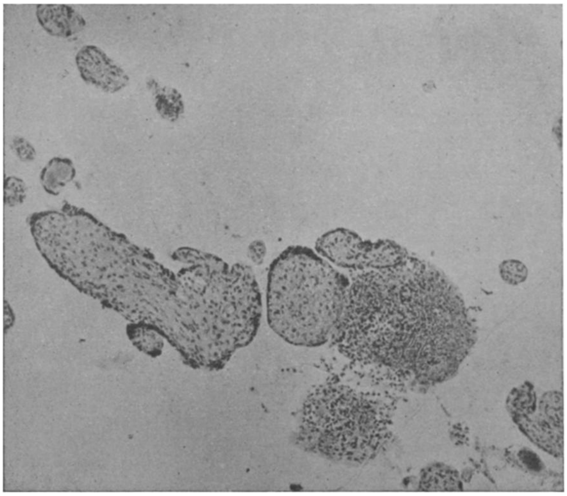

FIG. 5.—Earliest stage of intervillous tubercle. Agglutination-thrombus on chroionic villus. Syncytium is lost at base of thrombus.

Turning to the literature for information as to the nature of decidual tuberculosis, we find that the earlier observations on placental tuberculosis are wholly lacking in this respect. Up to the time of Runge's paper (1903) the only placental lesions described were those affecting the chorionic villi. Lehmann had, it is true, found in his first case a small area of round cells in the decidua which he regarded as tuberculous but he was unable to demonstrate the presence of any tubercle bacilli. Runge regarded his own case as the first one in which tuberculous lesions of the decidua were definitely shown to exist. His description, so far as it goes, coincides in all respects with that given above of my two cases. In the basal decidua he found sharply circumscribed areas staining more intensely with eosin and hematoxylin than the surrounding tissue. Around the periphery of these round cells in process of karyorrhexis and chromatin fragments were present, while the centers consisted of a finely granular detritus without round cells or nuclear fragments. No epithelioid cells or Langhan's giant-cells were found, although serial sections were made. Staining for tubercle-bacilli showed great numbers of the bacilli in and between the round cells and in the necrotic centers. These lesions were present chiefly in the basal decidua and in greatest numbers on the uterine side of Nitabuch's fibrin band. In a decidual septum extending in between the chorionic villi a similar area was found. In the lowest layer of the decidua in the neighborhood of the uterine glands some resemblance to epithelioid formation was seen.

Runge comments upon the failure of the decidua to form characteristic tubercles of epithelioid cells and giant-cells. Contrasting this absence of reaction with the practically universal formation of tubercles in other tissues of the body, he attempts to explain the phenomenon by the temporary character of the decidua and its slight capacity for proliferation, the latter being shown also in the rarity with which tumors develop in the decidua. That epithelioid cells may be found in the tuberculous lesions in the deepest layer of the decidua bears out the above view, since this portion of the decidua retains to a greater degree its original character and is not destroyed after birth.

In a case of abortion during the fourth month Westenhoeffer found a tuberculous focus in the decidua from which, according to his belief, an acute miliary tuberculosis of the mother developed. While the lesion is not sufficiently described, the changes in the decidua appear to have been essentially the same as those described by Runge.

Schmorl and Geipel found decidual lesions in one of their nine cases of placental tuberculosis. These were of the same character as those described by Runge, consisting of focal necroses containing tubercle bacilli; and lacking the characteristic tubercle formation. Giant-cells were found only in the deepest layers of the decidua.

In Wollstein's case the decidua showed extensive caseation, in some places extending throughout its entire thickness and into the muscle coat. No mention is made of epithelioid or giant-cells, but small tubercles with cheesy centers were found in the uterine musculature. Since no tubercles of the decidua were mentioned, it is fair to conclude that they were not present.

It will be seen, then, that in all of the cases of placenta tuberculosis in which the lesions of the decidua are mentioned, the latter have been of a uniform character, presenting as a caseation necrosis associated with thrombosis and without epithelioid and giant-cell formation. In common with Runge I believe that the failure of decidual tissue to form tubercles can be explained only by the peculiar character of the decidual cells. His explanation, however, does not seem to me to be wholly adequate. More lies behind this phenomenon than the temporary character of the decidua. Accepting the view that decidual cells are transformed stroma cells, in their peculiar transformation the cells have lost the power of responding to ordinary "irritants," in much the same way that the cells of a sarcoma have lost it. In two cases of secondary tuberculous infection of sarcoma seen by the writer the sarcoma-cells had undergone a caseous necrosis without the formation of giant-cells or epithelioid cells. True tubercles were found only in the remains of the original connective tissue of the affected part in one of the cases. In the other they were present only in the connective tissue of the trabeculae, the sarcoma being of the alveolar type. As decidual tissue has sometimes been called a "physiological sarcoma," the analogy is strengthened by the similarity in the absence of a granulomatous reaction to tuberculous infection. My explanation, then, is that the stroma cells in their transformation into decidual cells have already passed into an epithelioid form, and are incapable of further proliferation under the action of such stimuli as tubercle bacilli.

Runge and Schmorl and Geipel regard the thrombosis of the decidual vessels and sinuses as secondary to the tuberculous lesions in the decidua. In my opinion the decidual lesion is pratically always primarily a vascular one, the endothelium being first involved. The hyaline and agglutination thrombi are formed coincidently with, or immediately after, the injury to the endothelium and before the involvement of the neighboring decidual cells. The larger fibrin-masses are formed secondarily. Extensive thrombosis may be the immediate etiological factor of the abortion or premature birth. Congestion of the decidual sinuses (so-called decidual hemorrhages), infarcts of the decidua and chorion, etc., may be caused by the blocking of the placental sinuses.

The tuberculous thrombi are so characteristic that in a section stained with hematoxylin and eosin they readily catch the eye by the contrast they offer to the ordinary thrombus of the placental sinuses. They form the chief diagnostic feature of the microscopical examination for decidual tuberculosis. As their importance has been entirely overlooked by Runge and Schmorl and Geipel, I take this opportunity of emphasizing it. Aside from their serving as an aid to diagnosis, these thrombi are to a certain extent protective in localizing the primary lesion. Tubercle bacilli, however, spread through the wall of the injured vessel and the necrosis extends into the surrounding tissue. It is, of course, possible that bacilli may pass out into the decidua and give rise to a primary lesion outside of a blood-vessel. Runge believed this to occur, but in my cases the decidual lesions were apparently all primarily vascular.

The thickening of the walls and the obliteration of some of the decidual vessels noted by Runge and believed by him to be inflammatory in character and secondary to the tuberculous process may be found in the normal decidua in the later months of pregnancy. These changes are a part of the physiological maturity and beginning involution of the decidua. When occurring prematurely, as in Runge's case in the fourth month, they are to be regarded as evidences of a premature retrogression. Such changes are especially common in cases of maternal syphilis. Runge thought that these vascular conditions were responsible for the thrombosis seen in his case, but I do not believe this to be the correct interpretation.

The entire absence of giant-cells from the decidual lesions may be regarded as strong proof that they are not formed from lymphocytes. Lymphocytes were numerous in both decidual and chorionic lesions, giant-cells were present only in the latter. If they can be formed from lymphocytes there would be no reason why they should not occur in the decidua. Since they do not here, and since they occur only in association with epithelioid cells, the evidence is, I think, practically conclusive that they arise only from stroma cells. Likewise, the decidual lesions offer proof that epithelioid and giant-cells are not formed from vascular endothelium.

Summing up the chief characteristics of tuberculosis of the decidua, the following conclusions seem of importance:

1. Tuberculosis of the decidua consists primarily in a local lesion of endothelium with the formation at the point of injury of a hyaline or agglutination thrombus.

2. Extension of the process consists in the gradual formation of an area of caseous necrosis, a round-cell infiltration with subsequent karyorrhexis and a formation of fibrin throughout the focus of necrosis.

3. Tuberculosis of the true decidua differs from that of other organs and tissues in the absence of any tubercle-formation. Epithelioid and giant-cells are not formed.

4. The absence of giant-cells from the tuberculous lesions of the decidua may be taken as an argument against their formation from lymphocytes or endothelium.

5. The failure of the decidua to form epithelioid cells may be explained on the ground that the decidual cells in their transformation from stroma cells have lost the power of reacting to ordinary irritants.

B. INTERVILLOUS TUBERCLES.

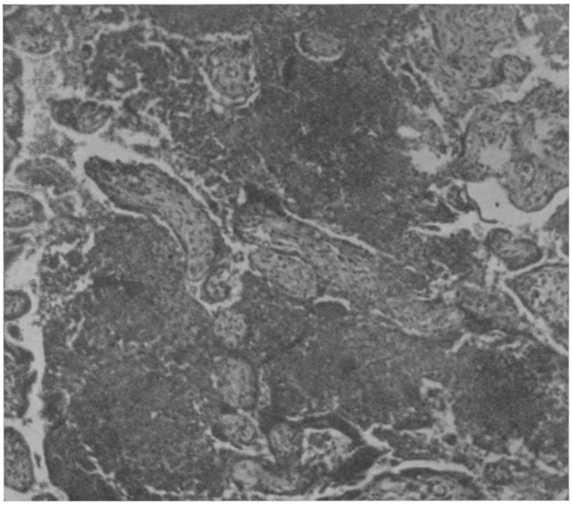

FIG. 6.—Tuberculous agglutination-thrombi in intervillous spaces.

Throughout the intervillous spaces there were small, round, deeply staining areas, composed of a finely granular or hyaline substance, containing lymphocytes and polymorphonuclear leukocytes in varying stages of disintegration. The majority of these areas were about the size of a small pinhead, or somewhat smaller. They took the eosin stain more heavily than the hyaline fibrin masses found normally in the intervillous spaces; but the fragmentation and diffusion of the chromatin of the nuclei of the leukocytes gave to many of them a bluish or violet tinge. Through their regular outline, deeper staining, and the constant presence of disintegrating leukocytes they attracted the eye at once as presenting features distinct from those of the normal intervillous thrombi. In their general characteristics they resembled in every respect the hyaline thrombi of the decidual vessels. When stained according to Weigert's fibrin method they showed the presence of fibrin, but the greater portion of the hyaline substance was shown by various stains, as well as by the different transition stages found, to consist of agglutinated red-blood cells and blood plates. The staining for tubercle-bacilli with carbol-fuchsin and methylene-blue showed varying numbers of the bacilli in the thrombi, as well as free bacilli in the intervillous blood-spaces.

In single sections these tuberculous thrombi often appeared lying between or adjacent to villi covered with syncytium, showing apparently no pathological changes. In other cases they appeared to be lying free in the blood-spaces. Serial sections, however, showed that in all cases they were attached to a villus at some point where the syncytium had either completely vanished or appeared as a swollen hyaline layer devoid of nuclei. In many cases the necrotic syncytium presented a finely granular appearance, suggesting a beginning caseation. A similar change was seen in the center of many of the thrombi. In those cases in which the syncytium was entirely absent the thrombus rested directly upon the stroma of the villus, which in many instances showed distinct evidences of epithelioid proliferation at the point of contact. Epithelioid cells and typical Langhan's giant-cells were found extending from the stroma of the villus into the thrombus. All stages of this process were found, from thrombi containing a single giant-cell or one or more epithelioid cells to those completely converted into epithelioid tubercles and showing a beginning caseation. In other words, the thrombi were being organized by epithelioid tissue arising from the stroma of the villi, and were thus changed into typical tubercles. Giant-cells were very numerous and very large. In some cases they could be seen extending out into the thrombus while still attached to the stroma of the villus. In many thrombi the only evidence of epithelioid change was found in solitary giant-cells; and these, though often apparently occupying the center of the thrombus had long

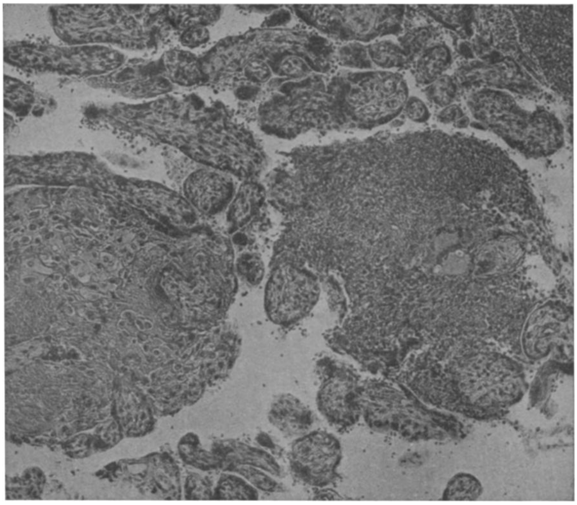

FIG. 7.—Intervillous tuberculous thrombus. First step in formation of tubercle. Giant-cell arising from stroma of small villus that is nearly wholly denuded of its syncytial covering.

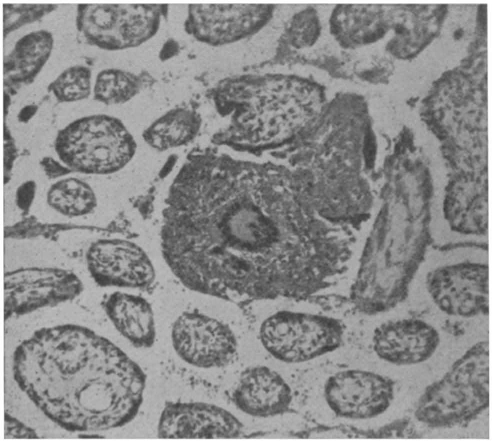

FIG. 8.—Intervillous aggultination-thrombus attached to villus where syncytium is lost. Contains one large giant-cell.

protoplasmic processes continuous with the stroma of the villus. In those thrombi resting upon an intact necrotic syncytium no giant-cells or epithelioid cells could be found. No connection could ever be demonstrated between the syncytium and a giant-cell, and not the slightest evidence could be obtained tending to prove the yncytial origin of the latter. Likewise, no evidence could be found of the origin of the epithelioid or giant-cells from lymphocytes. *On the other hand the evidence seems conclusive that they have a common origin in the stroma of the villi.*

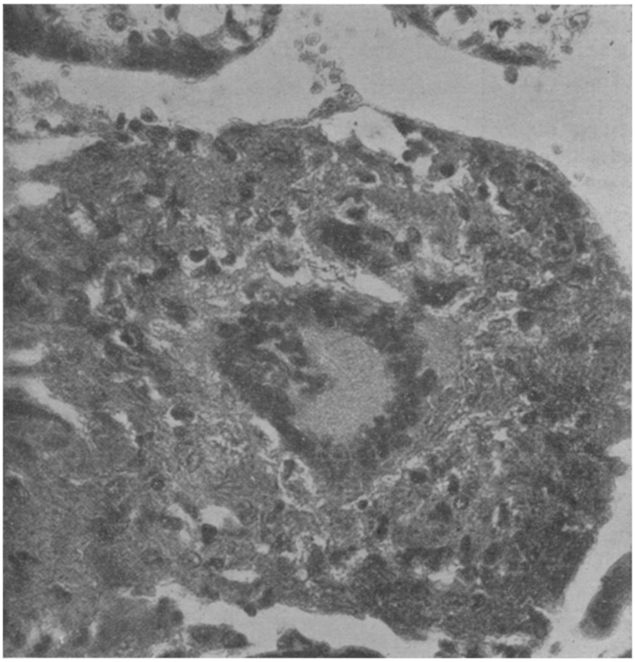

FIG. 9.—High-power view of giant-cell shown in Fig. 8.

The histogenesis of the intervillous tubercles may, therefore, be concisely stated as follows: There is first a lesion of the syncytium of the nature of a degeneration or necrosis, produced by the action of the tubercle bacilli lodging upon the surface of the villus. Upon the damaged syncytium there is deposited from the maternal blood a collection of leukocytes, red-blood cells, and blood-plates, giving rise to a hyaline or agglutination-thrombus. The next step is the epithelioid organization of the thrombus from the stroma of the villus, and the tubercle thus formed later suffers caseation. It is worthy of remark that the caseous process usually does not begin in the center of the thrombus or tubercle but adjacent to the villus, thus indicating that this is the older part of the tubercle.

In my former paper I expressed the view that the syncytium appeared to possess some resistance to the action of the tubercle bacillus, since some of the thrombi appeared to rest upon an apparently normal syncytium. The study of serial sections since made has demonstrated the occurrence of syncytial lesions in all such cases, and I am now forced to the conclusion that the syncytium does not show any greater resistance to the action of tubercle bacilli than does the vascular endothelium in any part of the body. *The placenta has no especial protection against tuberculosis. In the event of tubercle bacilli gaining entrance to the maternal blood-stream the chances in favor of a placental localization are as great as those of any other organ.* In fact, it is a question as to whether the chances of placental infection are not greater, the large size of the placental blood-spaces and the slowness of the circulation probably favoring the deposit of bacilli carried in the blood.

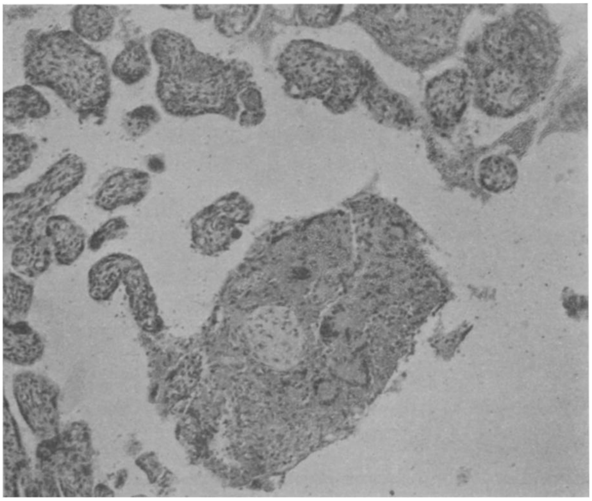

FIG. 10.—Full development of intervillous tubercle. Thrombus nearly wholly organized by epithelioid and giant-cells arising from stroma of villus. Syncytium wholly lost.

In the article written with Kockel, Schmorl expressed the view that the epithelioid cells might arise from the chorionic epithelium. In his more recent article with Geipel he has abandoned this view, and now believes that they arise either from the lymphocytes or from the fixed cells of the stroma of the villi. He was, however, unable to decide definitely as to their origin. He regards it as strange that the granulation-tissue, in case it does arise from the stroma, does not extend into the substance of the villi, but, on the contrary, grows outward, sometimes appearing to surround a villus that preserves still its original outlines. Such an outward growth does not always occur alone; many villi showed also an epithelioid ingrowth into the villus. Serial sections show, also, that the epithelioid tissue surrounding such a villus may arise from the stroma at some point either below or above the plane in which the given section was cut, or may have originated in the stroma of a neighboring villus. The outward growth is easily explained by the fact that the developing colony of tubercle bacilli is outside of the villus in the thrombus, and the conversion of the thrombus into a tubercle by an outward growth from the stroma of the villus is carried out according to the laws of chemotaxis and organization.

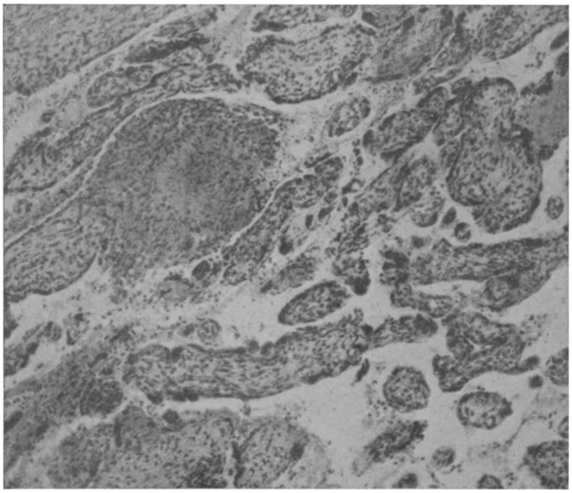

FIG. 11.—Intervillous tubercle with beginning caseation. Note continuity with stroma of villus at point of attachment.

While not absolutely denying the possibility of an origin of epithelioid cells from the lymphocytes included in the tuberculous thrombus, my cases show nothing to support such a view, but, on the contrary, all appearances favor their origin from the stroma-cells. The fact that many of the thrombi contained in their centers one large giant-cell apparently having no connection with the villus led me, in my first paper, to believe that giant-cells might arise from the white cells included in the thrombus, but my further studies favor wholly their connective-tissue origin. It may be asked if the lymphocytes in the intervillous thrombi have the power of producing epithelioid cells, why have not those found in the thrombi of the decidual vessels? The conditions are the same; but in one case we have an abundant formation of epithelioid cells, even in the smallest sized thrombi, while in the decidual thrombi such a formation is wholly wanting. This phenomenon, to my mind, is a very strong argument against the lymphocytes as a source of epithelioid cells in the formation of placental tubercles.

Conclusions.—The intervillous tubercles are the result of a primary lesion of the syncytium, caused by the growth of tubercle bacilli upon the surface of the villus. At the point of injury there is formed an agglutination thrombus which undergoes an epithelioid organization from the stroma of the villus, and the tubercle thus formed suffers caseation.

There is no evidence that epithelioid or giant-cells are formed either from the syncytium or from lymphocytes. All the findings favor their origin from the connective-tissue of the villi.

C. INTRAVILLOUS TUBERCLES.

In many villi tubercles were found arising in the stroma of the villus independently of any lesion of the syncytium or of any intervillous thrombosis. These intravillous lesions varied from a single giant-cell to epithelioid tubercles involving a part or nearly the whole of the villus and showing more or less advanced caseation. Caseous foci without epithelioid cells also occurred in the stroma of some of the villi. All the caseous areas contained tubercle-bacilli, and these were also found free in the spaces of the stroma of villi showing no pathological changes whatsoever. Even in villi whose stroma had for the greater part been replaced by epithelioid cells the syncytium showed no change. Only when the caseation had reached the subsyncytial layer of stroma did the syncytium become necrotic, and coincident with this change there always occurred a thrombosis at the site of the injured chorionic covering.

The presence of intravillous tubercles in the absence of syncytial lesions and thrombus-formation must, I think, be taken as strong evidence that the bacilli have passed through the syncytium without damaging it, and have set up their characteristic changes first in the stroma of the villus. The absence of thrombi upon the syncytium must be accepted as indicating that the syncytium is not involved, or, at least, not to any perceptible extent. The question of main importance here is the route by which the tubercle bacilli have reached the stroma-spaces. They must either have penetrated the syncytium without damaging it, or their presence in the villi may be the result of a retrograde metastasis from some other lesion involving chorionic vessels and liberating bacilli into the fetal circulation.

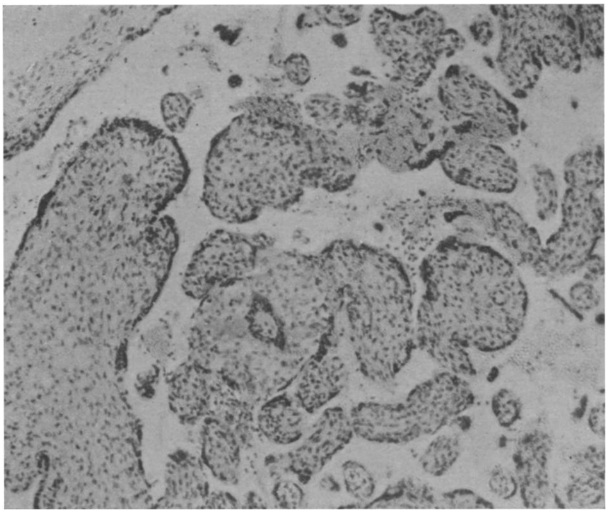

FIG. 12.—Intravillous tubercle. Giant-cell in interior of villus. No thrombosis

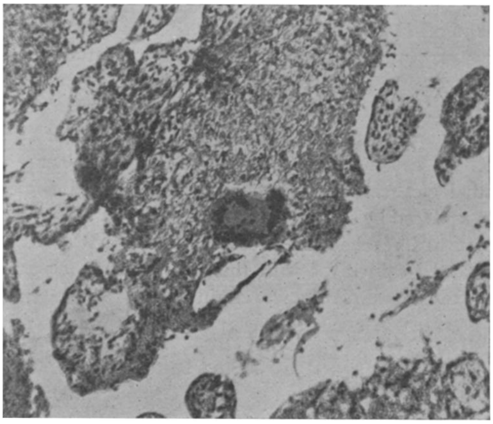

FIG. 13.—Intravillous tubercle. Giant-cell beginning caseation.

Schmorl regards the intravillous tubercle as very rare, having seen it but once in his set of cases. He considers two explanations, an entrance of bacilli through a defect in the syncytium or an infection from the fetal stream, either through direct metastasis after passing through the fetal body or through a retrograde transportation. Although not so numerous as the intervillous tubercles the intravillous lesions were common in my case. As described above, their character is essentially the same as that of the intervillous. There is first a localized necrosis, followed by an epithelioid proliferation of the neighboring fixed cells, forming a tubercle which eventually caseates. From the intervillous tubercle they are usually easily distinguished by the absence of a thrombus or by its minor prominence as compared with the changes in the villus itself. While it is not possible absolutely to decide the question, the fact that some villi develop tubercles in their stroma without showing in serial sections any evidence of a syncytial lesion inclines me to the belief that bacilli may pass the syncytium without injuring it. In the absence of

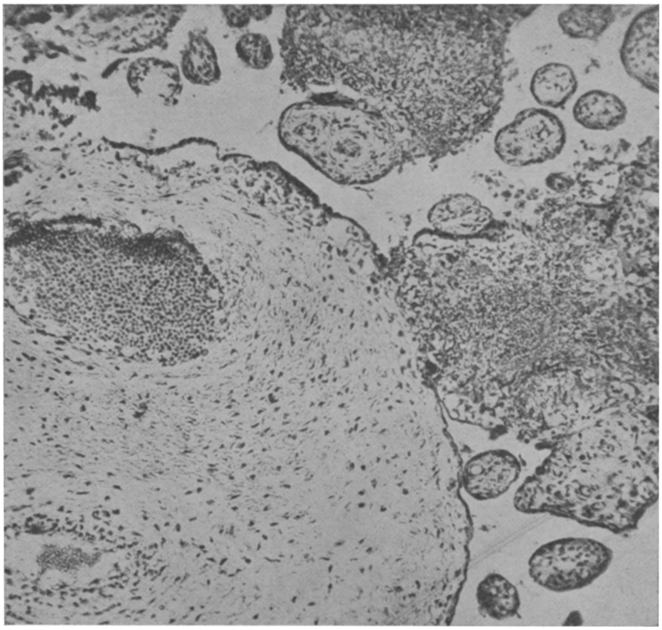

FIG. 14.—Intravillous tubercles with caseation.

tubercles in the organs of the fetal body, it does not seem likely that the chorionic villi would alone show tubercles if the dissemination occurred by metastasis direct through the fetal blood-stream. A retrograde transportation seems still less likely.

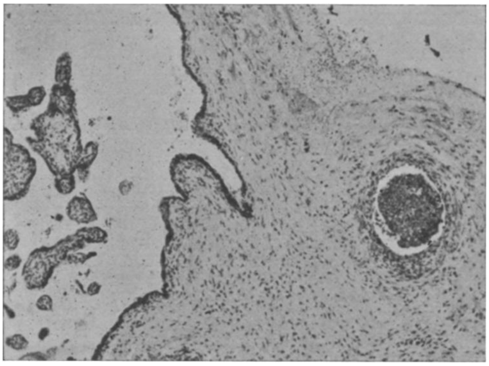

FIG. 15.—Intravascular chorionic tubercle. Agglutination-thrombus in chorionic vessel. Showed beginning epithelioid organization.

Conclusion.—Intravillous tubercles are less common than the intervillous ones. They may occur without apparent lesion of the syncytium and without the occurrence of thrombus-formation on the surface of the villi. It is, therefore, probable that tubercle-bacilli can pass the chorionic epithelium, leaving it unhurt, and set up tubercles within the substance of the villi.

D. INTRAVASCULAR CHORIONIC TUBERCLES.

Of still rarer occurrence were tubercles and tuberculous thrombi in the vessels of the chorion. The thrombi were either obturating or parietal, and were in all respects like those of the intervillous spaces. Attached to the intima of some of the larger chorionic vessels there were deeply staining hyaline or granular masses containing chromatin fragments. At the point of attachment to the wall the endothelium and subendothelial layer showed beginning necrosis. Tubercle bacilli were demonstrated in these thrombi. In the development of a tubercle the epithelioid cells arose in the vessel-wall.

E. CHORIO-AMNIOTIC TUBERCLES.

Secondary involvement of the amnion by large caseating or epithelioid tubercles of the chorion was seen a few times. The portion of the amnion lying in the neighborhood of the chorionic tubercle was thickened, infiltrated with lymphocytes, and showed a beginning caseation. Tubercle bacilli were contained in the caseous area. Similar lesions were twice found by Schmorl.

SUMMARY.

1. Tuberculosis of the placenta manifests itself in five forms, according to location: (1) Decidual; (2) Intervillous; (3) Intravillous; (4) Intravascular chorionic; (5) Chorio-amniotic.
2. In all forms the primary lesion is a *necrosis* of the cells at the point of bacillary growth, either upon the syncytium or endothelium, or in the decidua or stroma of the villi.
3. Lesions of syncytium or endothelium lead to the formation of hyaline or agglutination thrombi. These may become converted into tubercles through an epithelioid proliferation of neighboring fixed cells, and the tubercles so formed become caseous.
4. Decidual tuberculosis is characterized by necrosis of the decidual tissue and thrombosis of the sinuses without the formation of giant- or epithelioid-cells. Tubercles are not formed from the decidual cells.
5. The syncytium of the chorionic villi is no more immune to the action of tubercle bacilli than is the vascular endothelium in any part of the body.
6. There is some ground for the belief that tubercle bacilli may pass through the syncytium without causing injury to it.
7. The evidence afforded is against the formation of giant-cells from lymphocytes, endothelium, or syncytium but is in favor of their origin from connective-tissue cells.

In conclusion, the histological study of placental tuberculosis throws important light upon the general nature of the primary lesion produced by tubercle bacilli. The view advocated by Baumgartner and others that the tubercle bacillus causes primarily a cell-proliferation is flatly contradicted by the findings in tuberculosis of the placenta. Here it is clear that the primary lesion is in all cases a *necrosis* of cells at the point of bacillary development. The formation of a tubercle through a secondary cell-proliferation of connective-tissue cells immediately about the primary necrosis occurs wherever there are connective-tissue cells at the point of primary necrosis. In the case of the decidua the tuberculous lesion never gets beyond the stage of primary necrosis, cell-proliferation not taking place, so that decidual tubercles are not formed. The tubercle is, therefore, a secondary formation, inflammatory in nature, and reparative and protective in function.

REFERENCES.

1. LEHMANN. *Deutsch. med. Wchnschr.*, 1893, 19, p. 200.
2. RUNGE. *Archiv f. Gyn.*, 1903, 68, p. 388.
3. SCHMORL AND GEIPEL. *Münch. med. Wchnschr.*, 1904, 1, p. 676.
4. WARTHIN AND COWIE. *Jour. Infect. Dis.*, 1904, 1, p. 140.
5. WESTENHOEFFER. *Deutsch. med. Wchnschr.*, 1903, 29, p. 221.
6. WOLLSTEIN. *Archives of Pediatrics*, 1905, 22, p. 321.